

Optically Active 1-Hydroxy-3-Substituted Succinimides for Enantioselective Peptide Synthesis

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Optically active 1-hydroxy-3-substituted succinimides were prepared in good yield. The enantioselectivity was evaluated based on specific rotation of dipeptides. 1-Hydroxy-3-substituted succinimide esters of *Z*-alanine were treated with *D,L*-ethyl alaninate to indicate 70 and 90% diastereomeric excess of *L-L* and *D-D* isomers respectively.

Introduction

Optically active peptides have been prepared by condensation of optically active *N*-blocked amino acids or peptides with optically active amino acid esters or peptide esters. There have been many studies of new acyl activating reagents and new methods for peptide synthesis.

We have reported "enantioselective peptide synthesis" by use of optically active 3-hydroxyhydantoins¹⁾ and *N*-hydroxytartrimidates²⁾, that is to say, optically active peptides are prepared effectively from *DL*-amino acid. There have been only a few studies of enantioselective peptide synthesis^{3~5)}.

In the present paper, further examples of optically active 1-hydroxysuccinimides containing hydroxyl, acetoxy and acetamido groups on the 3-position were designed to examine

not only the possibility of enantioselective reaction but also the effect of substituents on the enantioselectivity thereof.

Preparations were carried out using dicarboxylic acids such as *L*(-)-aspartic acid and *L*(-)-malic acid as starting materials (scheme 1).

N-Carbobenzyloxyaspartic anhydride⁶⁾ was treated with benzyloxyamine at 0°C for 4 hr in THF and then left at room temperature for 24 hr to give *N*-carbobenzyloxyaspartic acid monobenzyloxyamide **1** in 92% yield. The half amide **1** was converted to 1-benzyloxy-3-carbobenzyloxyamidossuccinimide **2**. After decarbobenzyloxylation of **2**, 3-acetamidossuccinimide **4** was obtained by treating **3** with acetic anhydride at room temperature for 24 hr.

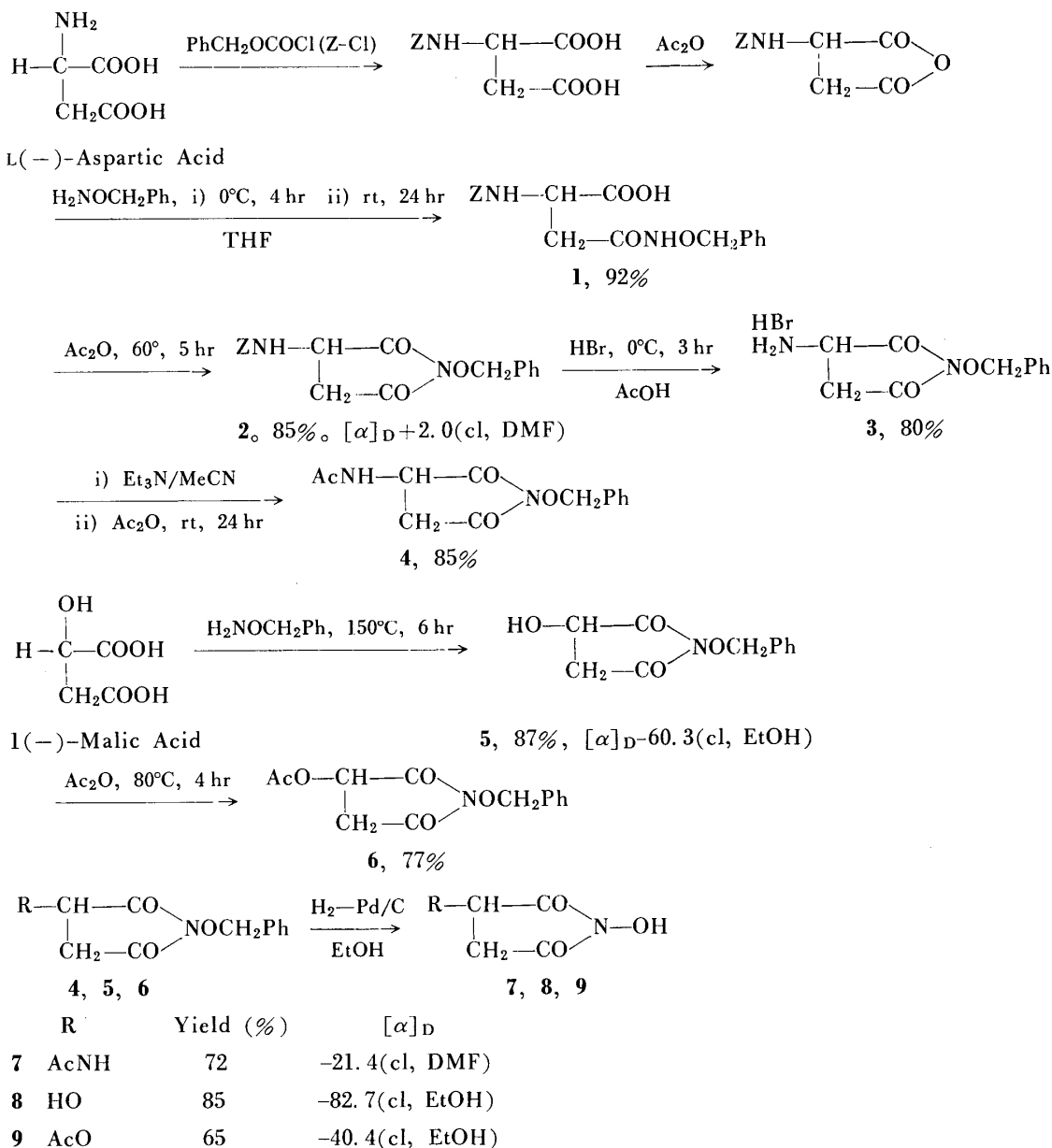
Malimides **5** and **6** were prepared from malic acid by the published method²⁾. Debenzylation of 1-benzyloxysuccinimides **4**, **5** and **6** gave optically active 1-hydroxy-3-acetamidossuccinimide **7**, 1,3-dihydroxysuccinimide **8** and 1-hydroxy-3-acetoxysuccinimide **9** respectively in good yields.

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Scheme 1.



The enantioselective peptide synthesis was carried out by use of 1-hydroxysuccinimides **7**, **8** and **9** in the active ester method (scheme 2).

A preparation of 1-hydroxysuccinimide esters⁷⁾ of Z-amino acids was carried out at 0°C for 24 hr in THF in the presence of dicyclohexylcarbodiimide (DCC). The THF solution of the ester thus obtained was added dropwise to DL-ethyl alaninate at 0°C in THF-

MeCN and then stirred at 0°C for 24 hr.

The results are summarized in Table. Optical yields were calculated based on specific rotation of dipeptides. In the Table, positive and negative signs of optical yields indicate L- and D-selectivities respectively.

The selective reaction of malimide esters of Z-L-alanine ((Z-L-Ala-**8** and Z-L-Ala-**9**) with racemic alaninate produced the same extent of diastereomeric excess of L-L isomer (Z-Ala-

Schem 2.

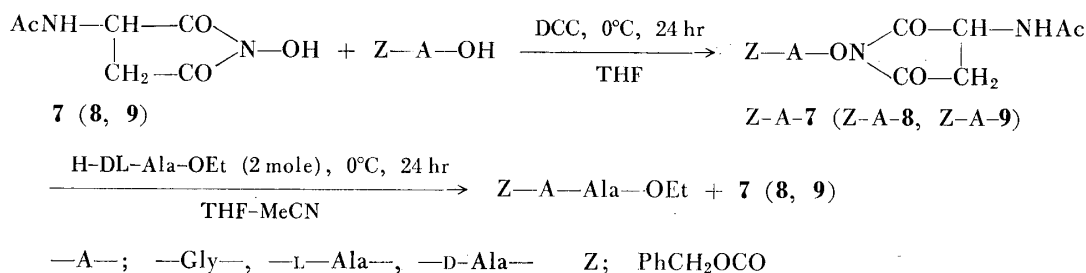


Table. Enantioselective Peptide Synthesis

Dipeptide R	Z-Gly—Ala—OEt			Z-L—Ala—Ala—OEt			Z-D—Ala—AlaOEt
	7(AcNH)	8(OH)	9(AcO)	7(AcNH)	8(HO)	9(AcO)	7(AcNH)
Yield (%) ^{a)}	86	82	85	100	100	91	94
[α] _D ^{b)}	+2.8	0	+1.0	-27.1	-34.7	-35.0	+40.0
L-Form (%)	44.8	50.0	48.2	67.5	83.8	84.3	4.4
O. Y. (%) ^{c)}	-10.3	0	-3.6	35.0	67.6	68.6	-91.2

a) based on Z—A—OH

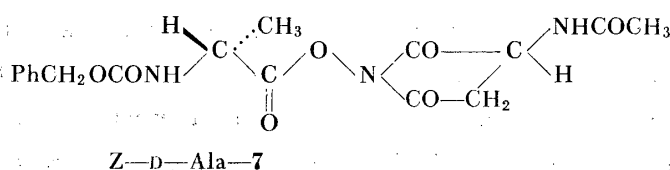
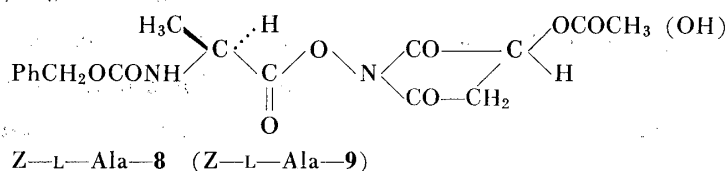
b) c 1, EtOH

c) O. Y. (Optical Yield) was calculated by using [α]_D of Z—Gly—Ala—OEt (L; -27.0, D; +27.0) and Z—Ala—Ala—OEt (L—L; -42.4, L—D; +4.8, D—L; -11.8, D—D; +42.4). O. Y. (%) = 100(L-D)/(L+D)

Ala-OEt, 68% and 69% respectively), regardless of substituents varied on the 3-position. However, the malimide ring did not affect enantiomeric excess of Z-Gly-Ala-OEt.

It was considerable that aspartimide ring itself would also select L-isomer in racemic alaninate and afford higher diastereomeric excess of L-L isomer (Z-Ala-Ala-OEt) because aspartimide and malimide rings had the same configuration. The aspartimide ring, however, did not lead the L-selectivity contrary to the

expectation. The selective reaction of Z-Gly-7 with racemic alaninate proceeded with 10% enantiometric excess of D-isomer (Z-Gly-Ala-OEt) and the reaction of Z-D-Ala-7 achieved 91% diastereomeric excess of D-D isomer (Z-Ala-Ala-OEt). The selective reaction of Z-L-Ala-7 remained lower diastereomeric excess (35%) of L-L isomer (Z-Ala-Ala-OEt). The fact shows the D-selectivity might be effected by the aspartimide ring, and the D-selectivity caused by Z-D-alanyl group and the L-selecti-



vity caused by Z-L-alanyl group.

The selectivity governed by the malimide **8** including hydroxy group was similar to the selectivity governed by the malimide **9** including acetoxy group. On the other hand, the selectivity controlled by the aspartimide ring was superior to the selectivity controlled by the malimide ring. Thus, there is no difference in the selectivity by difference in bulkiness between hydroxyl and acetoxy group whereas a wide difference in the selectivity between acetoxy and acetamido group which have comparable bulkiness.

Experimental

Preparation of N-Carbobenzyloxyaspartic Acid Monobenzyloxyamide **1**.

Benzyloxyamine (0.73 g) was added dropwise to N-carbobenzyloxyaspartic anhydride in THF at 0°C and stirred at 0°C for 4 hr and at rt for 24 hr. THF was evaporated and the residue was recrystallized from ethyl acetate-hexane (1.89 g, 86%): mp 129–32°C; IR (KBr) 3260, 3180, 1700, 1660, 736, 694 cm⁻¹; NMR ((CD₃)₂SO) δ 4.20 (1 H), 4.68 (2 H), 4.94 (2 H), 7.20 (5 H), 7.40 (2 H); Found: C, 61.38; H, 5.50; N, 7.52. Calcd for C₁₉H₂₀N₂O₆: C, 61.28; H, 5.41; N, 7.52.

Preparation of 1-Benzyloxy-3-carbobenzyloxyamidossuccinimide **2**.

A suspension of N-carbobenzyloxyaspartic acid monobenzyloxyamide **1** in acetic anhydride was heated at 50–60°C for 3 hr. The residue distilled out acetic anhydride was crystallized from ethyl acetate-hexane, and then recrystallized from the same solvent (1.45 g, 81%): mp 106–9°C; IR (KBr) 3280, 1795, 1720, 1690, 750, 700 cm⁻¹; NMR ((CD₃)₂SO) δ 2.84 (2 H), 4.16 (1 H), 4.94 (2 H), 5.52 (1 H), 7.24 (5

H); Found: C, 64.00; H, 5.11; N, 7.85. Calcd for C₁₉H₁₈N₂O₅: C, 64.40; H, 5.12; N, 7.19; $[\alpha]_D +2.0$ (cl, DMF).

Decarbobenzyloxylation of **2**.

A suspension of **2** (2.26 g) in acetic acid (10 ml) was cooled and added hydrogen bromide saturated in acetic acid (25 ml). The solution was stirred for 2 hr in an ice bath. After added ethyl ether, the ppt was filtered and washed with ethyl ether until removed the odor of hydrogen bromide. 1-Benzyloxy-3-aminosuccinimide hydrogen bromide **3** obtained was dried (1.78 g, 80%): mp 185–7°C; IR (KBr) 2920–2800, 1803, 1715 cm⁻¹.

Preparation of 1-Benzyloxy-3-acetylaminosuccinimide **4**.

1-Benzyloxy-3-aminosuccinimide hydrogen bromide **3** (2.75 g) was allowed to react with triethylamine (1.4 ml) at rt for 5 hr in acetonitrile and then to the mixture added acetic anhydride (15 ml). The solution was left at rt for 24 hr. The residue condensed was washed with ethyl ether for several time, dissolved in ethyl acetate, and dried over sodium sulfate. After evaporation, the residue was recrystallized from ethyl acetate-hexane (1.37 g, 85%): mp 121.5–3.5°C; IR (KBr) 3280, 1800, 1725, 1635, 750, 700 cm⁻¹; NMR ((CD₃)₂SO) δ 1.86 (3 H), 3.38 (2 H), 3.85 (1 H), 5.02 (2 H), 7.42 (5 H), 8.58 (1 H); Found: C, 42.23; H, 4.70; N, 16.50. Calcd for C₆H₈N₂O₄: C, 41.86; H, 4.68; N, 16.28.

Preparation of 1-Benzyloxy-3-hydroxysuccinimide **5**.

A suspension of L(–)-malic acid (5 g) in xylene was heated with benzyloxyamine at 150°C for 6 hr and after cooled the mixture, the ppt was filtered. The ppt was recrystallized from ethyl acetate-cyclohexane or ethyl acetate-

chloroform (7.2 g, 87%): mp 122.5–4.0°C; IR (KBr) 3420, 1790, 1700, 750, 700 cm^{-1} ; NMR ($(\text{CD}_3)_2\text{SO}$) δ 4.14 (2 H), 4.62 (2 H), 5.20 (1 H), 5.27 (1 H), 6.84 (5 H); Found: C, 59.87; H, 5.03; N, 6.28. Calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4$: C, 59.72; H, 5.01; N, 6.33.

Acetylation of 1-Benzoyloxy-3-hydroxysuccinimide **5**.

1-Benzoyloxy-3-hydroxysuccinimide **5** (1.4 g) was suspended in acetic anhydride and heated at 80°C for 5 hr. After cooled, the ppt was filtered, washed with ethyl ether and recrystallized from ethyl acetate–hexane (1.32 g, 77%): mp 114–6°C; IR (KBr) 1805, 1725, 1720, 750, 700 cm^{-1} ; NMR ($(\text{CD}_3)_2\text{SO}$) δ 2.04 (3 H), 2.80 (1 H), 2.97 (1 H), 4.96 (2 H), 5.36 (1 H), 7.32 (5 H); Found: C, 59.06; H, 4.88; N, 5.32. Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_5$: C, 59.31; H, 4.98; N, 5.32.

Debenzylation of **4**, **5** and **6** (Preparation of **7**, **8** and **9**).

Ethyl alcohol solution of benzyloxysuccinimide derivative (**4**, **5** and **6**) was treated with hydrogen gas in the presence of 5% palladium carbon until hydrogen gas was never spent. **7**: mp 188–9°C; IR (KBr) 3160–3040, 1795, 1720, 1640 cm^{-1} ; NMR ($(\text{CD}_3)_2\text{SO}$) δ 1.82 (3 H), 2.88 (1 H), 2.56 (2 H), 8.52 (1 H); Found: C, 42.23; H, 4.70; N, 16.50. Calcd for $\text{C}_8\text{H}_8\text{N}_2\text{O}_4$:

N_2O_4 : C, 41.86; H, 4.68; N, 16.28. **8**: mp 157.0–8.5°C; IR (KBr) 3160–3040, 1780, 1690 cm^{-1} ; NMR ($(\text{CD}_3)_2\text{SO}$) δ 2.35 (1 H), 2.99 (1 H), 4.33 (1 H), 6.21 (1 H); Found: C, 36.73; H, 3.80; N, 10.66. Calcd for $\text{C}_4\text{H}_5\text{NO}_4$: C, 36.65; H, 3.84; N, 10.69. **9**: oil; IR 3240–3160, 1800, 1725, 1700 cm^{-1} ; NMR ($(\text{CD}_3)_2\text{SO}$) δ 2.04 (3 H), 2.72 (1 H), 2.92 (1 H), 5.30 (1 H).

References and Notes

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- 6) E. Schröder and E. Klieger, *Justus Liebigs Ann. Chem.*, **673**, 208 (1964).
- 7) It is possible to isolate 1-hydroxysuccinimide esters. e. g.; 1-Hydroxy-3-acetamidossuccinimide ester of Z-glycine: Yield 87%; mp 105–8°C; IR (KBr) 3240, 1795, 1730, 1650 cm^{-1} ; NMR ($(\text{CD}_3)_2\text{SO}$) δ 1.84 (3 H), 2.96 (1 H), 3.17 (2 H), 4.00 (2 H), 4.88 (2 H), 7.08 (5 H), 7.64 (1 H), 8.41 (1 H); Found: C, 53.02; H, 4.68; N, 11.58. Calcd for $\text{C}_6\text{H}_{17}\text{N}_3\text{O}_7$: C, 52.89; H, 4.72; N, 11.57.